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(54) Title: DELIVERY OF SUGAR AS AN ACTIVE INGREDIENT

(57) Abstract

The present invention includes a method and product for controlled-delivery of sugar as a bio-affecting agent. The invention includes sugar in a physical condition which makes it bio-available to a mammalian host. The sugar is physically associated with a controlled-release system in a manner which provides a pre-selected profile of bio-availability to the host. Preferably the sugar is in the form of shearlite particles, and a convenient product for delivery of the sugar includes confections such as a nutrition bar, and unit dosage forms, e.g., tablets and capsules.

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DELIVERY OF SUGAR AS AN ACTIVE INGREDIENT

BACKGROUND OF THE INVENTION

The present invention relates to the art of delivering substances for bio-availability to mammals, especially humans. In particular, the present invention concerns the delivery of sugar as an active ingredient.

Carbohydrates constitute one of the primary sources of energy for humans. Generally, carbohydrates make up about 50%-70% of the normal human diet. Carbohydrates enter the human biological system as glucose which is a ready precursor to fat and which appears to play an important role as a systemic ingredient in several metabolic pathways. In addition, blood sugar levels play a role in the onset of hunger sensations.

It has been desirable to be able to deliver a source of energy to the human body in a manner which enables the host to utilize the energy as it is made available without unnecessary storage of calories or "bulking up" on carbohydrates. Thus, it would be advantageous to provide a continuous source of energy to the body, and the muscles in particular over a prolonged period of time, or at a particular point in time. The ability to supply energy at pre-selected times and rates is particularly important when the host is engaged in rigorous physical activity such as sustained athletic events, or when the host is dieting to suppress the onset of hunger. Moreover, it is also important to deliver energy to the body at a pre-selected time or rate without creating an instantaneous oversupply, i.e., spike, of glucose level in the blood stream.

A reduced level of systemic glucose is believed to contribute to appetite and perceived satiety. Increased glucose utilization appears to activate the neural satiety center and decrease the activity of the feeding center.

For example, U.S. Patent No. 4,210,637 to Wurtman, *et al.* discloses a composition and method for suppressing appetite for carbohydrate calories while elevating the level of calories consumed as protein. The composition includes a combination of

tryptophan and carbohydrate. Tryptophan increases brain serotonin level. Carbohydrates, such as sucrose, dextrose, starch, fructose, invert sugar, dextrins, and sugar polymers, e.g., polyose, xylitol and mixtures thereof: 1) increase the level of insulin secretion, and 2) decrease the levels of other neutral amino acids normally found in plasma such as leucine, isoleucine, tyrosine, phenylalanine, and valine, which compete with tryptophan for uptake in the brain. Consequently, the level of serotonin in the brain is increased. Thus, when a carbohydrate, e.g., sugar, is administered with tryptophan, the appetite of host is suppressed.

Furthermore, glucose levels in humans is very important to control the effects of diabetes mellitus. Diabetes patients suffer from a deficiency in insulin, a hormone which stimulates glucose uptake by cells. It is important that a diabetic carefully control the level of glucose available in the body. While too much glucose can be harmful to the patient, a low glucose level can also have serious adverse affects including diabetic shock and even death.

Delivery of energy to a host at a pre-selected rate and treatment of the conditions described above, require administration of sugar to the host in a manner which renders glucose available to the hosts biosystem (hereinafter referred to as bio-availability in a carefully regulated pattern. For example, a non-regulated dosage of sugar which creates a spiked profile of glucose bio-availability could create insatiable craving in a host undergoing treatment to suppress appetite, e.g., an obese patient. Moreover, a similar non-regulated dose could cause a patient to fall into a coma.

To-date regulated systems for delivering glucose involve structural (i.e., mechanical) and, in some cases, electrical devices. These solutions suffer from undue complexity, unreliability, cost, unsightliness, and in some cases require invasive surgical techniques for implementation.

Thus, a need currently exists for controlled delivery of carbohydrate, especially sugar, to a mammalian host in accordance with a selected profile of bio-availability without the drawbacks of delivery systems currently available or under

consideration. It is an object of the present invention to provide, among other objects, a manner which meets this need.

SUMMARY OF THE INVENTION

The present invention is a method and a product for the controlled delivery of sugar, as a bio-affecting agent, to a mammalian host, especially a human host. The advantage provided by the present invention is that sugar becomes available to the biological system of the host, i.e., bio-available, in accordance with a pre-selected profile.

The present invention requires that sugar, which has been defined more fully hereinbelow, be provided in a physical condition which makes it readily available to the host. Furthermore, a controlled-release system is physically associated with the sugar to provide the pre-selected and pre-determined release profile of bio-availability. In its simplest manifestation, the sugar is combined with a sustained release component as a controlled-release system.

The present invention encompasses the use of a controlled-release system which can include a component selected from the group consisting of an instantaneous release component, a delayed release component, and a sustained release component. The controlled-release system can also include a combination of each of the components set forth above. These components are described hereinafter in greater detail. In one preferred embodiment of the invention the controlled-release system includes a combination of at least two of the components set forth above.

In another preferred embodiment of the present invention, sugar is provided in the form of shearlite particles. Shearlite particles, which can also be referred to as microspheres, has been fully described in co-pending U.S. Application Serial No. 08/330,412 filed October 28, 1994. The advantages of using sugar in the form of shearlite particles is that the particles can be easily manufactured according with the process disclosed in the co-pending application which enables one to produce particles which are highly uniform in size and shape. Such

shearlite particles can be efficiently and predictably coated to form a component of a controlled-release system.

The methods of the present invention include rendering sugar bio-available to a host according to a pre-selected release profile. Specific applications include a method of maintaining blood sugar levels as well as a method of suppressing appetite. Furthermore, inasmuch as sugar is a very efficient source of energy, the present invention also includes a method for providing energy to a host at a predetermined point in time or over a predetermined period of time in accordance with a pre-selected release profile.

Products of the present invention include, but are not limited to, comestibles, confections such as nutritional bars and unit dosage forms, e.g., capsules, or tablets.

As a result of the present invention a product and method of providing sugar as a source of energy and as a systemic ingredient for use in metabolic pathways in the host is conveniently provided. The sugar can be made bio-available in a number of ways without the requirement the host to unnecessarily store calories which usually results in a build up of fat in the body. Energy can also be provided without undue peaks and valleys in levels of glucose in the blood stream as is currently common.

Furthermore, as a result of the present invention, complex and unreliable systems and unnecessary techniques for regulating delivery of sugar known to date are eliminated.

For a better understanding of the present invention, together with other and further objects, reference is made to the following description, and its scope will be pointed out in the appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is a method for delivering sugar to a mammalian host, especially a human host, in a controlled manner so that a desired profile of bio-availability can be provided at a predetermined point in time or over a pre-selected period of time. Since, sugar is the active ingredient in the present

invention, it must be in a physical condition which makes it readily bio-available to a mammalian host, especially a human host.

Another element of the present invention is a controlled-release system which is physically associated with the sugar. The physical association between the controlled-release system and sugar in the present invention simply means that the controlled-release system and the sugar are combined in such a way as to provide a highly predictable pre-selected release profile of bio-availability as a result of normal interaction of the bio-system on the sugar/controlled-release system combination.

The controlled-release system of the present invention can include components such as an instantaneous release component, a delayed release component, and a sustained release component. Furthermore, the controlled-release system can include a combination of these components to provide the desired release profile of bio-availability. Preferably, the sugar/controlled-release system combination is included in a confection such as a nutrition bar or a dosage form (e.g., a capsule, tablet, or flowable dosage).

Sugar as used herein means those substances which are based on simple crystalline mono- and di- saccharide structures, i.e., based on C_5 and C_6 sugar structures. Such sugars include sucrose, fructose, lactose, maltose, and sugar alcohols such as sorbitol, mannitol, maltitol, etc. Combinations of sugars can also be used. With respect to a preferred embodiment the sugar should be able to be transformed under liquiflash conditions into shearlite particles. A preferred choice of sugar in the present invention is sucrose.

As previously described, the present invention also includes a controlled-release system which is combined physically with the sugar to provide a pre-selected release profile of bio-availability to a host, preferably a human host.

Controlled-release system is used herein to describe a composition which can include one or more components for making an active ingredient available to the biological system of a host. The controlled-release system can include an

instantaneous release component, a delayed release component, a sustained release component, and combinations thereof.

An instantaneous release component is self-explanatory in that it refers to an ingredient which promotes or enhances immediate release to the biosystem of the host. The present invention includes the possibility of transforming sugar to a physical condition which has a unique release profile different from the release pattern of the same sugar without such transformation. The instantaneous release component can be an additional ingredient which enhances dispersion of sugar throughout the bio-system. An example of an instantaneous release component is a surfactant.

A delayed release component is an ingredient which prevents the active ingredient, i.e., sugar, from being made available to the host until some time after initial administration. When administration is oral, the delayed release component prevents release of sugar until some time in the future. Delayed release components include, but are not limited to, polymeric coating(s), biodegradable coating(s), etc.

A sustained release component is an ingredient, or combination of ingredients, which permits release of active ingredients to the host at a certain level over a period of time. Sustained release can be provided by use of coatings which include gels, waxes, fats, emulsifiers, combinations of fats and emulsifiers, polymers, starch, etc., as well as the above in combination with polymeric coating(s) or other biodegradable coatings.

The method of effecting each type of release can be varied. For example, the sugar can be associated physically (which also includes being chemically associated or bound) with one or more of the components set forth above. Alternatively, the active ingredient can be a coated, laminated, encapsulated etc., such as discussed below. Regardless of the method of providing the desired release profile, the present invention contemplates use of one or more of the components described above.

With respect to the sustained release component, the patent and scientific literature is replete with various sustained release (SR) methods and formulations.

For common methods of obtaining SR systems, see Sustained and Controlled Release Drug Delivery Systems, Robinson, Joseph R., Ed., PP 138-171, 1978, Marcel Dekker, Inc. New York, NY. For example, it is known to fill polymeric capsules with a solid particle which can, in turn, be made to release active ingredient according to a known pattern or profile. Such particles can also be made to have more than one release profile so that over an extended time the combined release patterns provide a pre-selected profile.

Furthermore, heterogeneous matrices, such as, for example, compressed tablets, control the release of active agents either by diffusion, erosion of the matrix or a combination of both. Other SR systems focus on the fabrication of laminates of polymeric material and active agent which are then formed into a sandwich, relying on diffusion or erosion to control release of the active agent. Additionally, it is generally known that heterogeneous dispersions or solutions of active agents in water-swellable hydrogel matrices are useful in controlling the release of the agent by slow surface-to-center swelling of the matrix and subsequent diffusion of the active agent from the water-swollen part of the matrix.

During dissolution of a controlled-release matrix tablet, the dosage form generally remains as a non-disintegrating, slowly eroding entity from which the active agent leaches out, through a diffusion controlled process. Conventional SR formulations are generally designed to release their actives over an extended period of time, usually 8-24 hours. Conventional SR formulations use waxes or hydrophilic gums as the primary carriers to prolong the release of the active ingredients. In conventional wax matrix tablet formulations, the active agent is dispersed in the wax matrix in the molten state. Conventional waxes and waxy materials used in pharmaceutical formulations are carnuba wax, spermaceti wax, candellila wax, cocoa butter, cetosteryl alcohol, beeswax, partially hydrogenated vegetable oils, ceresin, paraffin, myristyl alcohol, stearyl alcohol, cetyl alcohol and stearic acid. They are generally used in amounts of about 10 to about 50% by weight of the total formulation.

Hydrophilic gums have also been known to be reasonably effective as SR carriers for both high-dose and low-dose active agents. Typical hydrophilic gums used as SR carrier materials are acacia, gelatin, tragacanth, veegum, xanthin gum, carboxymethyl cellulose (CMC), hydroxypropl methyl cellulose (HPMC), hydroxy propyl cellulose (HPC) and hydroxy ethyl cellulose (HEC). Generally these materials are present in amounts of about 10 to 50% by weight of the final formulation.

Starch USP (potato or corn) is commonly used as a component in conventional tablet or hard shell capsule formulations. It generally functions in conventional applications as a diluent or as a disintegrant in oral dosage forms. Starch paste is also often used as a binder in these products. Various modified starches, such as carboxymethyl starch currently marketed under the trade name Explotab or Primojel are used both in tablets and capsules as disintegrating agents. The literature discloses that native and modified starches are useful in promoting rapid release of active agents from solid oral dosage forms, and, thus, could be used as an instantaneous release component.

Additionally, native starch has been used in some instances as a binder to produce granulations of active ingredients. More recently, pregelatinized starch has been reported as being useful as an SR matrix for theophylline formulations by Herman and Remon, "Modified Starches as Hydrophilic Matrices for Controlled Oral Deliver; III Evaluation of Sustained-Release Theophylline Formulations Based on Thermal Modified Starch Matrices in Dogs," in International Journal of Pharmaceutics, 63 (1990) 201-205. In sustained release applications several types of modified starch were mixed with anhydrous theophylline (60:40 W/W) as well as with silicon dioxide (Aerosil 200) and sodium benzoate. In prior papers, (International Journal of Pharmaceutics, volumes 56 (1988) 145-153; 56 (1989) 51-63; and 56 (1989) 65-70) the authors discussed the use of both drum-drying and extrusion of native starches to obtain partial or full pregelatinization.

Polymers useful as coatings in the present invention are those deposited as solution coatings and dispersion coatings which can be used to coat particles, including shearlite

particles. Plasticizers are also normally included in both organic solvent systems and aqueous systems. The present invention includes the use of known polymers, plasticizers, dispersions, etc. which can be used in or as coatings for sugar particles.

In general however, processes known in the art for preparing coated particles can be used with the present invention.

As a result of the high uniformity and narrow size distribution, shearlite particles permit the use of substantially less coating materials to produce the intended effect. Thus, with a single complete but thin coat, efficient controlled-release can be effected. This however, does not preclude shearlite particles from being coated with multiple layers of active and controlled release coatings.

In all controlled release technologies it is desirable to be able to incorporate the active ingredient in a single dosage unit to provide the pre-selected release profile without deteriorating the active ingredient. Moreover, the dosage unit should be able to deliver the active ingredient without interfering with the pre-selected release profile.

In the present invention sugar is the active ingredient which is combined with one or more of the delivery components to provide a host with a pre-selected profile of bio-availability of sugar. The term physically associated is used herein to describe the nature of the combination of sugar and delivery or release component, and the term includes all features of the relationship between the sugar and the delivery component, e.g., structural, chemical, mechanical, etc. of primary importance is that the combination renders sugar bio-available to the host according to a pre-selected profile.

The profile can be selected to achieve one of many goals. For example, the release of sugar can be engineered to provide a sustained source of readily useable energy; or to participate in the metabolic system(s) which controls appetite to suppress (or even enhance) appetite; or to ensure an acceptable level of blood sugar for a diabetic patient, or to provide a delayed

release of sugar as a useable energy. Other benefits are contemplated and can be achieved based on the desired objective.

In the case of providing a source of energy from the alimentary tract to augment physical activity, the pre-selected profile will require a dosage which is planned based on the time expected for the human system to digest a substance, e.g., generally not greater than about four (4) hours. If the host is not engaged in strenuous activity, the dosage can be reduced, or delayed until the energy source is required.

For an appetite suppressant the dosage rate can be similarly planned, and, if a co-active ingredient is administered proximally with the sugar, the dosage can be adjusted depending on the desired result. Additional co-active ingredients which are known for use as appetite suppressants include, but are not limited to, tryptophan (especially when used with an insulin-inducing carbohydrate), diethylpropion hydrochloride, mazindol, phentermine hydrochloride, fenfluramine hydrochloride (d-fenfluramine and the racemic *dl*-fenfluramin), fluoxetine hydrochloride, and phenylpropanolamine hydrochloride.

When the host is a diabetic, a sustained sugar release profile can be selected which delivers glucose at an even rate over several hours.

A particularly preferred embodiment of the present invention includes the use of sugar in the form of shearlite particles. As described in co-owned U.S. Patent Application Serial No. 08/330,412, sugar shearlite particles are discrete particles prepared by subjecting a solid sugar feedstock, capable of being transformed to a liquiform in the substantial absence of a dissolving medium, to liquiflash conditions to provide substantially unimpeded internal flow. The feedstock, thus reduced to unimpeded internal flow, is subsequently separated by natural mass separation of the flowing feedstock in the presence of shear force to form shearlite particles.

Shearlite particles prepared in accordance with the present invention are ideally suited for coating. They have a highly consistent spheroidal shape and the narrow range of size distribution causing the shearlite particles to flow evenly and easily and to be susceptible to even coating with a minimum

amount of coating material. Consequently, shearlite particles can be efficiently coated to obtain a corresponding consistently-coated product.

Liquiflash conditions are those conditions which provide transformation of a solid to a liquid state and then to the solid state (e.g., solid-liquid-solid) instantaneously. By instantaneously is meant less than seconds, preferably on the order of fractions of a second, and most preferably on the order of milli-seconds. Thus, certainly the transformation from solid to liquid to solid takes place in a time period of less than five seconds, preferably less than one second, and most preferably less than 0.1 seconds.

During this rapid transition, shear forces can act on the material to separate the feedstock while in liquiform. Thus, liquiflash conditions are the combination of temperature and force which induce the sugar feedstock to flow and re-solidify into a changed shape as it is being separated by the action of shear force. In preferred embodiments the size and the new shape of the particles are highly consistent. The shape is substantially spheroidal and the size distribution is very limited with only minor variations.

The discrete particles produced are preferably microspheres, which as used herein, means not greater than about 500 Fm, more preferably not greater than about 400 Fm, and most preferably not greater than about 300 Fm. In the preferred method of the present invention the liquiflash conditions are provided by a spinning head having a heated peripheral barrier with exit openings provided therethrough for passage of feedstock flowing under centrifugal force as described in U.S. Patent Application Serial No. 08/330,412, filed October 28, 1994 and hereby incorporated by reference.

According to the present invention the controlled release sugar can then be utilized to form numerous comestibles, including nutritional bars and the like. Additional ways of administering the active ingredient of the present invention to mammalian hosts are also contemplated.

EXAMPLES

EXAMPLE I
Sucrose Spheres

Sustained release sugar microspheres can be prepared by forming sugar particles or microspheres (shearlite particles), as taught and described in U.S. Patent Application No. 08/330,412. The sugar spheres (or plain sugar particles) may then be coated with coating materials such as Eudragit® E100 (7.5% ethocel) dissolved in a solvent of acetone and methanol in a ratio of 5:1.

EXAMPLE II
Coated Sugar Microspheres

A mixture of various coated, sustained release sugar particles (including coated shearlite particles) are combined in amounts such the release profile in the host body is sufficient to provide a sustained, elevated blood sugar level in the subject host (or to conform to a desired release profile).

The mixture of coated sugar particles include measured (predetermined) amounts of sugar particles which have been coated with different coatings. The different coatings will each provide their own, unique release profile. But when combined in various, predetermined amounts, or manner, the finished mixture will provide the desired release profile throughout the desired period of time.

The coated particles can be administered in any number of known forms, including nutritional bars, tablets, capsules, unit dose, etc.

Additionally, the sugar does not have to be coated. It just has to be made available to elevate, or maintain the host's blood sugar levels when desired.

Also, formulations of sustained release sugar could be coated onto a non-sugar bead or microsphere, or even a sugar (shearlite) particle.

WE CLAIM:

1. A comestible for controlled delivery of sugar as a bio-affecting agent coprising:

sugar in a physical condition which makes it bio-available to a mammalian host, and

a controlled-release system physically associated with said sugar to provide a pre-selected release profile of bio-availability to said host.

2. The comestible according to Claim 1 wherein said sugar is in the form of shearlite particles and said controlled-release system is coated over said shearlite particles.

3. A method of rendering sugar bio-available to a mammalian host according to a pre-selected profile comprising:

administering a combination of sugar in a bio-available condition and a controlled-release system physically associated with said sugar to release said sugar according to said profile.

4. The method according to Claim 3 wherein said sugar is in the form of shearlite particles and said controlled-release system is coated over said shearlite particles.

5. A method of maintaining blood sugar levels in a mammalian host according to a pre-selected profile comprising:

administering a combination of sugar in a bio-available condition and a controlled-release system physically associated with said sugar to release said sugar according to said profile.

6. A method of suppressing appetite in a mammalian host

comprising:

administering a combination of sugar in a bio-available condition and a controlled-release system physically associated with said sugar to release said sugar according to a pre-selected profile which is associated with appetite suppression.

7. A nutrition bar for controlled delivery of sugar as a bio-affecting agent comprising:

sugar in a physical condition which makes it bio-available to a mammalian host, and

a controlled-release system physically associated with said sugar to provide a pre-selected release profile of bio-availability oto said host.

8. A unit dosage for controlled delivery of a sugar as a bio-affecting agent comprising:

sugar in a physical condition which makes it bio-available to a mammalian host, and

a controlled-release system physically associated with said sugar to provide a pre-selected release profile of bio-availability to said host.

9. The unit dosage of Claim 8 which is a capsule.

10. The unit dosage of Claim 8 which is a tablet.